UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/724,833	12/02/2003	Thomas Nelson	17357.01302US	2811

38647 7590 05/19/2005

MILBANK, TWEED, HADLEY & MCCLOY LLP
INTERNATIONAL SQUARE BUILDING
1825 EYE STRET, N.W. #1100
WASHINGTON, DC 20006

EXAMINER	
ROOKE, AGNES BEATA	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 05/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/724,833	NELSON ET AL.	
	Examiner	Art Unit	
	Agnes B Rooke	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *13 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,22-29 and 34-41* is/are rejected.

7)☒ Claim(s) *18-21 and 30-33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/15/04; 01/12/04*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *March 10, 2005*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The previous action set on 09/13/2004 is vacated.

Applicant's election with traverse of Group I, Claims 1-27 and 39-41 in the reply filed on December 13, 2004, is acknowledged. The traversal is on the grounds that the search and/or examination of the claimed subject matter of Group I and Group II, and a search of apolipoprotein and therapeutic agent genuses would not impose a serious burden on the examiner. Therefore, the argument is found persuasive and the examiner rejoined Group I and Group II and withdrawn the election of species requirement.

Therefore, Claims 1-41 are pending and currently under examination.

This application claims benefit of 60/430,476, filed in 12/03/2002.

Objections to Claims

The name of "LDL" in the first claim must be spelled out.

Objections to Specification

Page 25, [00104] of the specification, states that *"LDL suspension is stable for at least 7..."* The time frame for the stability of suspension must be specified.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The "solid" lipid core must be more definitely defined in the claims, since it is not certain whether "solid" has high viscosity like gelatin or it is solid as wood.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-17, 22-29, 34-41 are rejected under 35 U.S.C. 102(b) as being anticipated by Versluis et al., Stable Incorporation of a Lipophilic Danorubicin Prodrug into Apolipoprotein E-Exposing Liposomes Induces Uptake of Prodrug via Low-Density Lipoprotein Receptor in Vivo, J. Pharmacol. Exp. Ther., (1999), 289(1), p. 1-7.

Versluis et al. made liposomes comprising a lipophilic derivative of daunorbucin, a chemotherapeutic agent (LAD). Cited at page 3, paragraph 2 of specification. [0009-0010] to page 4 [0012].

At page 2, right column, a mixture of egg yolk phopshatidylcholine (EYPC), ^{3}H-Cholesteryl oleate (^{3}H-CO) and LAD was sonicated to form

liposomes. The liposomes were subsequently incubated with ApoE. Therefore, the limitations of the method of producing LDL particles as set forth in Claim 34 is taught by Versluis et al. Claim 35 is also anticipated because the diameter was 29.3 (plus-minus 1.1) nM. See page 3, right column.

It is noted that at [0032] of the specification the artificial LDL particles comprising EYPC, cholesterol oleate, and ApoE3 form solid particles comprising a solid lipid core consisting of cholesterol, cholesterol esters, a random active agent, a middle layer consisting of the fatty acid chains phosphatidylcholine, and a surface layer consisting of phospholipids head groups and ApoE3. At [00103] EYPC and cholesteryl oleate dissolved in methanol and chloroform and evaporated under inert gas nitrogen at 4°C. In Versluis et al. the mixture of EYPC, ^{3}H-CO, and LAD, the solvent dichloromethane was also evaporated in nitrogen at 4°C. At [00103], the evaporated EYPC and cholesteryl oleate was hydrated using Tris-HCl buffer, at pH 8, containing 0.1M KCl and sonicated for 1 hr at 18 μM output under the natural gas nitrogen. This same procedure is performed by Versluis et al., except the inert gas argon was used. At [00104] the liposomes were incubated with ApoE for 30 minutes at 37°C at 1:10 ratio. This same procedure is performed by Versluis et al.

While liposomes are generally considered to be bilayers, See specification [0054], and the claims are drawn to an outer monolayer of phosphatidylcholine, it appears that the liposome of Versluis et al. comprise an outer PC monolayer because the method of making the liposomes as taught in Versluis et al. is nearly identical to the method taught in Example 2 in the instant specification.

Therefore, Versluis et al. teach an artificial LDL particle comprising an outer phospholipids monolayer comprising at least one apolipoprotein and a solid lipid core containing at least one therapeutic agent (Claim 1), wherein the apolipoprotein is ApoE3 (Claims 2 and 3). The outer phospholipids monolayer comprises an oxy sterol (^{3}H-cholesteryl oleate) (Claim 4). The therapeutic agent is danorubicin, a chemotherapeutic agent (Claims 5-8). The phospholipids of the outer phospholipids monolayer was phosphatidylcholine and the apolipoprotein is ApoE3 (Claims 9 and 10; and Claims 22-24).

The particle size of the liposomes of Versluis et al. is taught at page 3, right column, to be 29.3 (plus-minus 1.1) nM, which is a diameter of between 15 and 50 nM (Claim 11) and 20-30 nM (Claim 12). At page 2, right column, the density of the liposome of Versluis is 1.016 to 1.040 g/ml, which is between 1 and 1.07 g/ml (Claim 13) and 1.02-1.06 g/ml (Claim 14).

At page 4, left column, the half-life LAP incorporated into the liposomes was enhanced to about 30 minutes. Therefore, at 2 hours, 6.25% of the particle should remain in the serum (Claim 15).

Versluis et al. did not assess brain uptake of the LAD when they assessed the tissue distribution of LAD incorporated into liposomes (See Figure 4, for example). However, because the liposomes of Versluis et al. appear to be the same as the LDL particles claimed, one skilled in the art would surmise that the further characterization of the LAD liposome would inherently show that it was transported across the blood brain barrier (Claim 16) and had a 3-fold greater uptake specificity for brain when compared to liver (Claim 17).

At page 2, right column, the LAD liposomes where dialyzed against PBS, and therefore are compositions comprising the LAD liposome and a pharmaceutically acceptable carrier (Claims 25-27). The kit of Claims 39-41 are included because the composition was in a container and the instructions for use are not given patentable weight.

LAD consists of danorubicin linked to cholesteryl-oleate via tetra-peptide spacer. See page 2, column 1, paragraph 2. Therefore, Versluis et al. teach a conjugate of cholesterol and chemotherapeutic agent (Claims 28 and 29).

Versluis et al. administered the LAD liposomes to rats. See page 3, left column, paragraph 2. Therefore, Versluis et al. teach a method for delivering of a substance comprising administration effective amount of a composition comprising LAD liposomes and pharmaceutically acceptable carrier (Claims 36-38). Transport through the blood brain barrier would be inherent to the administration of the LAD liposome.

Claims 28 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Byun et al. (U.S. 6,245,753).

Byun et al. teach different amphiphilic heparin derivatives, for example, heparin-cholesterol conjugates (Claim 28), where those derivatives are used as anticoagulating agents (chemotherapeutic agents, Claim 29). See Abstract and column 6, line 57-58.

Claims 1, 5-9, 11-17, 25, 27, 39, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Westesen et al., Characterization of Native and Drug-Loaded Human Low Density Lipoproteins, J. of Pharmaceutical Sciences, (1995), 84(2), p. 139-147.

Westesen et al. state that LDLs consist of a hydrophobic core with cholesterol, cholesterol esters, and triglycerides, and a surface monolayer containing phospholipids, cholesterol, and apoprotein B-10. See page 139, left column.

Westesen et al. isolated LDLs from human plasma and loaded them with anticancer agents (chemotherapeutic agents), adriamycin 32 (AD32) and the M-mustard derivative WB4291. See page 139, right column, second paragraph.

At page 144, right column about half way down, Westesen et al. teach via the use of NMR that the lipid core of the AD32 loaded LDL is not solid, but is present as a liquid with a high viscosity at 31° and 98°C. In the specification at [0061] "solid core" is stated to comprise cholesterol, cholesterol esters, and triglycerides, as well as other agents. The term "solid" is not clearly defined, i.e. having high viscosity like gelatin or solid as in wood. Therefore, the examiner turned to Webster's New Collegiate Dictionary wherein solid is defined as being within an internal cavity, compact, neither gaseous or liquid, a substance that does not flow under moderate stress.

Thus, the hydrophobic core comprising cholesterol, cholesterol esters, and triglycerides as taught by Westesen et al. appear to be the same solid core as defined in the specification, i.e. comprising cholesterol, cholesterol esters, and

triglycerides. Even though Westesen et al. teach that the core is not solid but a high viscosity liquid, because the specification is silent regarding the metes and bounds of the term "solid," and the Dictionary provides a definition of which high viscosity can be attributed, the hydrophobic core of Westesen et al. is taken to be equivalent to that solid lipid core of the claims. Note also that the term "artificial" is not defined over the LDLs of Westesen et al. at [0053]. The specification states that "artificial LDL particles" mean a structure comprising a spherical phospholipids monolayer and a solid lipid core. Thus, to teach an LDL particle comprising an outer phospholipids monolayer comprising an apolipoprotein and a solid lipid core that contains a therapeutic agent (Claim 1), such as adriamycin, wherein the therapeutic agent is a chemotherapeutic agent (Claims 5-8). The LDL is most likely phosphatidylcholine because membranes are predominantly phosphotidylcholine (Claim 9).

The diameter of the AD32 LDLs of Westesen is 20nm (Table 64) and are therefore between 15 and 50 nm (Claim 11) and 20-30 nm (Claim 12). Then density of the AD32 LDL is 1.03-105, and is therefore between 1-1.07 g/ml (Claim 13) and 1.02-1.06 g/ml (Claim 14).

At page 139, right column, paragraph 3, last sentence, Westesen et al. note that the drug loaded LDL were originally prepared for a clinical trial. Therefore, the drug loaded LDL of Westesen et al. was placed into a composition without a pharmaceutically acceptable carrier (Claims 25 and 27).

The kit of Claims 39 and 41 are included in this rejection because the composition was in a container and instructions for use are given no patentable weight.

Claims 15-17 are being included in this rejection because it is inherent that the LDL be stable in serum for at least 2 hours, cross the blood brain barrier, and have 3-fold quarter uptake in the brain compared to the liver because the drug loaded LDL of Westesen et al. anticipates the claimed LDL particles having these qualities.

Conclusion

No Claims are allowed.

Claims 18-21 and 30-33 are objected to because they depended from rejected independent claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnes Rooke whose telephone number is 571-272-2055. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information about the PAIR system, see http://pair-

direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

AR

AR

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER